REMARKS

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed. Claims 1-8 and 11-13 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 1-8 and 10-14 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Halazy et al., WO 01/47920 in view of Bennett et al., *Current Opinion in Pharmacology* 2003, 3:420-425 (or Kaneto-I, Kaneto-II, Kaneto-III or Hotamisligil) and Gatlin et al., US 6,559,188. This rejection is respectfully traversed.

While Bennett, Kaneto-1, Kaneto-II, Kaneto-II and Hotamisligil teach that the JNK pathway may be involved in diabetes and insulin resistance, using various genetic evidence or biomolecular tools, these references do not teach that a JNK inhibitor would however treat such diseases. The Hotamisligil reference states on page S75, first column, that the JNK pathway is useful to treat diabetes and that salicylate inhibits the JNK pathway. However, it should be pointed out that Mihai et al, *J. Clinical Investigation* 11:1723-1724 (2001), a copy of which is submitted herewith, teaches that salicylate may increase insulin resistance (see first column on page 1723) and also negatively

influence insulin sensitivity (third column of page 1723) through other mechanisms. Hotamisligil also cites, on the same page, the JNK inhibitor SP600125 developed by Bennett, as a tool to demonstrate that the JNK pathway is involved in the development of diabetes and insulin resistance. However, SP600125 is reported in Bain et al., *Biochem J.*, 371:199-204 (2003), a copy of which is submitted herewith, to be a weak inhibitor of JNK. Bain teaches that SP600125 is non-specific since 13 of the 28 tested kinases were inhibited with similar or greater potency than JNK. See in particular Table 3, the middle of the first column on page 201, and middle of the second column on page 203. For instance, SP600125 is significantly more active on SGK, which is also known as being involved in diabetes and insulin resistance, as evidenced by the Kumar et al. *J. Am. Soc. Nephrol.* 10:2488-2494 (1999) reference, a copy of which is submitted herewith. SP600125 is also significantly active on AMPK, the target of metformin, a well known anti-diabetic agent. Thus, Bennett has not demonstrated that the positive results obtained with SP600125 (named cc105 in the Bennett reference) are due to JNK inhibition. It is altogether quite possible that these observed positive results are obtained via another biological pathway (in which SP600125 is active) known to be involved in diabetes.

Based on this knowledge, it would not be obvious to those of ordinary skill in the art that the compounds recited in the present method claims, even though they are known to be JNK inhibitors, would be effective in treating diabetes and insulin resistance. It is clear that compounds not structurally related, like SP600125 and the compounds of the present invention, have different selectivity profiles and thus different pharmaceutical properties. Thus, it cannot be deduced from the specific example of SP600125 that any JNK inhibitor, including the structurally unrelated compounds presently claimed, would have the same effect. It is further pointed out that it is not enough to have identified that the JNK pathway may be involved in diabetes in order to conclude that any JNK inhibitor would effectively treat diabetes, especially since there is much in the way of complex and unforeseeable mechanisms of regulation that may occur.

Accordingly, the combination of references cited and applied by the examiner simply cannot make obvious the presently claimed method using the recited compound for the treatment of type 2 diabetes.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their

allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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Appendix

The Appendix includes the following item(s):

- Mihai et ai, *J. Clinical Investigation* 11:1723-1724 (2001)

- Bain et al., *Biochem J.*, 371:199-204 (2003)

- Kumar et al. *J. Am. Soc. Nephrol.* 10:2488-2494 (1999)